MAYO CLINIC

Reprogramming of the Infant Brain by Surgery With General Anesthesia

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Consistently cited as one of the greatest discoveries of modern medicine, general anesthesia has garnered widespread respect and acceptance for its remarkable ability to safely render a person unconscious with nothing to show for it afterward but a short-lived hangover. However, beginning approximately a decade ago, studies began to challenge the premise that the brain is restored to its erstwhile pristine state after general anesthesia. Nowhere is the possibility of long-term alteration in brain function of greater concern than when an infant needs a procedure that requires general anesthesia. Accumulating preclinical data indicate that exposure to commonly used general anesthetic agents during key periods of brain development can lead to apoptotic neurodegeneration, synapse loss, and cognitive and behavioral deficits that persist as the organism matures.[1-4] In addition, neonatal anesthetic exposure alters neurogenesis and synaptogenesis in animals,[5-8] indicating that anesthetic medications influence neuroplasticity.[9] The brain is most vulnerable to this neurotoxicity and neuroplasticity during the brain growth spurt, which corresponds to a critical period of synaptogenesis and activity-dependent pruning and sculpting of synaptic architecture.[1,4] Because synaptogenesis in humans is believed to occur between late gestation and 3 to 4 years of age, then infants and newborns who require general anesthesia during these years are possibly at risk for cognitive or neurobehavioral sequelae, if the animal data can be extrapolated to humans.

This assertion brings us to the report by Sprung et al[10] in this issue of *Mayo Clinic Proceedings,* which reveals an association between general anesthesia during infancy and the development of attention-deficit/hyperactivity disorder (ADHD). These investigators retrospectively reviewed the hospital and school records of a well-characterized cohort of children born in Rochester, MN, between 1976 and 1982. They discovered the cumulative incidence of a diagnosis of ADHD was more than 2-fold greater by 19 years of age among children who underwent 2 or more procedures that required general anesthesia before the age of 2 years (7.3% in unexposed children vs 10.7% after 1 exposure vs 17.9% after ≥2 exposures).[10] Data from this investigational group and others had already suggested a link between general anesthesia during infancy and learning disability later in life.[11-13] The novel feature of the latest study by Sprung et al, however, is that it is the first to implicate general anesthesia and surgery as risk factors for ADHD, the most common neurobehavioral disorder of childhood. Inasmuch as ADHD reflects dysfunction of cortical networks,[14] this finding raises the sobering possibility that multiple procedures and general anesthetics reprogram the infant brain. Accordingly, Sprung et al[10] add new fuel to the conflagration that posits that general anesthesia for surgery in infancy comes at the price of cognitive and neurobehavioral disabilities in later life.

The work of Sprung et al[10] builds on an impressive array of studies from Mayo Clinic investigators addressing this topic. Retrospectively, they have repeatedly mined the database from the same cohort, albeit using different age ranges (exposure from 0-2 or 0-4 years of age) and end points (learning disability, defined variously by school performance, achievement tests, and/or need for an individualized educational program; and neurobehavioral disability, defined rigorously using research criteria for ADHD).[10-12] Regardless of the neurodevelopmental outcome chosen, the results of the Mayo Clinic studies are strikingly consistent: a single exposure to general anesthesia during a surgical procedure is not associated with an adverse cognitive outcome, but the risk of a subsequent cognitive or neurobehavioral abnormality is several-fold greater after multiple exposures.[10-12] Other investigators using an administrative database report similar associations, with children in the Medicaid program who underwent inguinal hernia repair having a greater risk of being diagnosed as having a behavioral abnormality.[13,15]

However, not all studies agree. Data from the Netherlands Twin Registry[16] identified no difference in group achievement test scores between exposed and unexposed twins, and another study from Denmark found no effect on academic performance in adolescence of hernia repair performed with the patient under general anesthesia in the first year of life.[17]

Retrospective, epidemiologic studies, such as that of Sprung et al,[10] represent an efficient and cost-effective way to gain insight into developmental events in humans that manifest in decades rather than days. Using this approach to study learning disabilities after surgery with general anesthesia, the Mayo Clinic investigators have already advanced our knowledge considerably, and this current report takes us further into the realm of possible linkages with emotional-behavioral syndromes.

However, retrospective designs that use clinical or administrative databases are encumbered by weaknesses that are acknowledged by these authors, both here and in their previous reports.[10-12] Among

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the concerns is that the cohort studied by Sprung et al[10] underwent surgery with anesthesia between 1976 and 1982. Much has changed since then. Halothane, the volatile anesthetic agent used in the Mayo Clinic cohort and others of that era, is rarely used today, and standards of anesthetic care are such that monitoring technologies unavailable then (pulse oximetry to detect hypoxia, capnography to prevent hypercarbia and hypocarbia, and end-tidal anesthetic agent monitoring) are routine now. Also, because male infants need surgery more often than female infants, the exposed population was disproportionately male (as is the case in most studies of infant surgery with anesthesia thus far). This gender bias is potentially important because the male brain may intrinsically be more vulnerable to certain insults than the female brain due both to hormone-dependent and hormone-independent factors, and males have a 3-fold higher risk of ADHD than females independent of exposure to a procedure that requires general anesthesia.[18,19] Moreover, persons with ADHD often have learning disabilities, further confounding the picture. Sprung et al[10] corrected for sex in their statistical model and analyzed a subgroup of ADHD patients without a learning disability and still found an association between multiple exposures to procedures with general anesthesia and ADHD, but patients and controls were not matched prospectively on these variables.

What everyone wants to know, of course, is whether surgery with general anesthesia causes learning disabilities and/or ADHD. Unfortunately, the work of neither Sprung et al[10] nor others using similar methods[10-13,15,17] can provide the definitive answer because the study designs are unable to disentangle the preexisting propensity for cognitive and neurodevelopmental disorders among children needing surgery with anesthesia from the effect of the general anesthesia and the surgery itself. Yet, it is revealing that the incidence of ADHD in this study, and learning disability in others, is higher only in infants who had 2 or more procedures that required anesthetics. Healthy infants seldom need surgery with general anesthesia once in 2 years, let alone 2 or more times. Of the 350 children who underwent surgery with anesthesia in the report by Sprung et al,[10] only 64 (18%) fell into the multiple-exposures category. As such, one need be cautious about drawing conclusions about associations of surgery with anesthesia during infancy and long-term disability when the cohort is so small. Furthermore, a child requiring multiple procedures with general anesthetics in the first 2 years of life is likely to be phenotypically different from unexposed children (eg, exposed children had a lower birth weight and gestational age and more comorbidities than unexposed children). Are we dealing with a chicken or egg problem? Is surgery with anesthesia causing cognitive or neurodevelopmental problems in children, or do infants who need multiple procedures have these problems ab initio? Prospective, randomized studies currently under way will most likely help unravel these issues but not for at least 5 years.

Multiple procedures with anesthetics also mean more drug exposure. To be sure, all eyes—and blame—thus far have been on the anesthetic agents, and for good reason. As discussed, animal data, including some from nonhuman primates, consistently and compellingly show that general anesthesia without surgery during a critical period of brain development can alter the structure and function of the brain.[1-8] Preclinical data also support the idea that longer exposures and drug combinations, conditions often replicated clinically, are worse in terms of neurodegeneration than single, brief exposures. So, anesthetic and sedative medications are by no means off the hook as potential developmental neurotoxins, particularly when long or multiple exposures to anesthetics are required. However, no one receives general anesthesia for the fun of it. The reason for long or multiple exposures to anesthesia is long or multiple procedures. These, in turn, typically reflect more complicated surgical illness. So, as Sprung et al[10] are careful to point out, surgery itself (and other noxious procedures) must be in the risk equation.

Surgery is a sensory assault. This is worrisome in the infant because in early childhood sensory experience is an important driver of brain wiring. At no time is the brain more malleable and exquisitely sensitive to a host of sensory and environmental influences than during the so-called critical period, when, impressively, simple sensory maneuvers (eg, eye closure or whisker trimming in neonatal rodents) profoundly and persistently alter the physical structure and wiring of the brain.[20] Sedatives and general anesthetics may also be capable of inducing such rewiring, but so too can other events that occur in the setting of infant illness, hospitalization, and surgery.

Stress, pain, and inflammation come immediately to mind. In animals, neonatal stress affects brain structure and function by decreasing neurotrophic factors, neurogenesis, and synapse formation.[21] Likewise, noxious stimuli in early life enhance pain sensitivity and remodel pain pathways.[22] Inflammation is particularly concerning. Invasive procedures cause tissue injury, which produces both peripheral and central inflammatory responses, including increases in cytokines, such as interleukin 1β and tumor necrosis factor α in the plasma, cerebrospinal fluid, and brain, and increases the reactivity of immunocompetent cells in the brain.[23,24] This is important because proinflammatory proteins

modulate synaptic plasticity and play major roles in sculpting synaptic architecture during development.[25] Indeed, a neonatal bacterial infection reprograms the brain such that hippocampus-dependent memory falters in adulthood in the face of a subsequent immune challenge.[26] Circumstantial clinical evidence also supports this concept. Neonatal sepsis increases the risk of developing a neurodevelopmental disorder later in life, stress during infancy increases vulnerability to cognitive deficits and neuropsychiatric maladies in adulthood, and painful procedures in infancy, including surgery, are associated with greater pain sensitivity and analgesic requirements subsequently.[27-29] This does not prove that noxious procedures cause subsequent neurobehavioral disorders any more than do data showing an association with exposure to general anesthesia, but the concept fits with the prevailing view that many neuropsychiatric disorders that manifest in later life have their origins in developmental programming by environmental events in infancy.[30] Therefore, it seems prudent to think of surgery and other stress- or pain-inducing procedures, together with the general anesthetics that make them bearable, as environmental events that, like many others, individually or together reprogram the infant brain.

This conceptual framework has important implications for understanding and potentially mitigating cognitive and neurobehavioral disorders associated with surgery and anesthesia in infants. If nothing else, it gets us beyond the narrow perspective that if we just tinker with anesthetic conditions the problem will resolve. Given laboratory evidence for anesthetic-induced neurodegeneration and neuroplasticity and the awareness that certain anesthetic agents (eg, the α_2-adrenergic receptor agonist dexmedetomidine and xenon) are less neurotoxic than others,[31,32] anesthetic conditions may be important. As such, practice changes revolving around anesthetic management are worth exploring; however, because they address only a small, temporally limited aspect of the bigger picture, these may be insufficient to materially improve cognitive and neurobehavioral outcomes of infants subjected to multiple operations with general anesthetics.

Considering the seriousness of the presumed problem and complexity of human brain development, we advocate taking a broader view. Infant pain management deserves attention, as do low-cost, low-risk, nontechnical interventions aimed at minimizing noise, reducing sleep disruption, and limiting periods of maternal separation (which is one of the most potent stressors of infancy). Some of these are being tested in infant critical care units, where improving neurodevelopmental outcome of preterm infants is a challenge, and that experience may inform work in infants with less serious illness.[33] Finally, assuming an epigenetic role of inflammation, anti-inflammatory agents, including anesthetic medications with a strong anti-inflammatory profile, may be a way forward. This approach has recently been successful in mitigating short-term learning impairment associated with tibial surgery in adult rodents,[23,24] but whether it would be beneficial during neurodevelopment is unknown.

For parents, health care professionals, and regulators, all of this raises difficult questions for which there are no easy answers. One encouraging insight from the human studies, including that of Sprung et al, is that a single, relatively brief operation with a general anesthetic during infancy seems not to affect subsequent cognitive and neurobehavioral development (although a single long exposure may be problematic).[10-12] Because most operations in infants are brief, this is welcome and reassuring news for parents confronting the scary prospect of a child requiring a general anesthetic for a procedure. Otherwise, we are still largely in the dark.

Until we know whether the outcome is preordained by virtue of patient characteristics or influenced by specific features of anesthesia and surgery and what those features might be, efforts to make procedures that require general anesthesia in infants safer, no matter how sensible and well intentioned, will be on soft ground. That is why additional preclinical and clinical research, including prospective, randomized, and controlled trials and neuroimaging of infant brain structure and function after surgery and anesthesia, is urgently needed. In the meantime, it is essential to recognize that there is still no proof that neonatal exposure to surgery with general anesthesia causes adverse neurodevelopmental outcomes in humans. Therefore, other than taking sensible precautions (eg, exposure as brief as possible, maternal contact as much as possible), the decision to proceed with surgery with anesthesia in an infant is best made based on what is known about the indications for and benefits of the procedure and general anesthetic rather than what is unknown but feared.

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